REMARKS/ARGUMENTS

Applicants have cancelled claims 75-79 without prejudice to or disclaimer of the subject matter encompassed thereby. Applicants expressly reserve the right to file continuing applications or take other such appropriate measures to seek protection for the inventions encompassed by the cancelled subject matter.

Claims 68 and 88 have been amended to provide a lower limit to the recited dosage range, support for which may be found in the specification on page 90, first full paragraph. Applicants have also amended the title and abstract to be indicative of the compositions of the present claims, support for which may be found throughout the specification and in the originally filed claims. Accordingly, no new matter has been added by way of these amendments to the claims and specification.

Claims 67-74 and 80-88 are currently under examination. Reconsideration of these claims is respectfully requested in view of the following remarks. The Examiner's comments in the Office Action are addressed below in the order set forth therein.

The Objections to the Specification and Claims Should Be Withdrawn

The Examiner has objected to the title and abstract for not being descriptive of the claims. Applicants have amended the title and abstract as described above. Accordingly, Applicants submit that these objections have been obviated and request that they be withdrawn.

The Examiner has objected to claims 75-79 as improper dependent claims for failing to further limit the subject matter of a previous claim. Applicants have cancelled claims 75-79. Accordingly, Applicants submit that these objections have been obviated and request that they be withdrawn.

The Rejection of the Claims Under 35 U.S.C. §112, Second Paragraph, Should Be Withdrawn

Claims 68 and 88 have been rejected under 35 U.S.C. §112, Second Paragraph, for indefiniteness. The Examiner interprets "less than about 5 mg" or "less than about 2.5 mg" as

reading on a dosage of 0 mg. Solely in the interest of expediting prosecution, Applicants have amended these claims to include a lower limit of about .5 mg. Accordingly, Applicants submit that this rejection has been obviated and request that it be withdrawn.

The Rejection of the Claims Under 35 U.S.C. §103(a) Should Be Withdrawn

Claims 67-88 have been rejected under 35 U.S.C. §103(a) as being obvious in light of Oberpenning *et al.* (*Curr. Opin. Urol.* 12:321-332 (2002)) in view of Madersbacher *et al.* (*BJU Intl.* 84:646-651 (1999)), Ikeda *et al.* (*Naunyn-Schmiedeberg's Arch. Pharmacol.* 366:97-103 (2002)), and Thor *et al.* (U.S. Patent App. Pub. No. 20060188575). This rejection is traversed for the reasons provided below.

Applicants do not believe that the Examiner has established a *prima facie* case of obviousness. Even if, *arguendo*, the Examiner has established a *prima facie* case of obviousness, evidence of unobvious or unexpected advantageous properties can rebut *prima facie* obviousness. *In re Chupp*, 816 F.2d 643, 646, 2 USPQ2d 1437, 1439 (Fed. Cir. 1987); *In re Papesch*, 315 F.2d 381, 137 USPQ 43 (CCPA 1963). The Federal Circuit has expressly stated that:

> One way for a patent applicant to rebut a *prima facie* case of obviousness is to make a showing of "unexpected results," i.e., to show that the claimed invention exhibits some superior property or advantage that a person of ordinary skill in the art would have found surprising or unexpected. The basic principle behind this rule is straightforward – that which would have been surprising to a person of ordinary skill in a particular art would not have been obvious.

In re Soni, 54F.3d 746, 34 USPQ2d 1684, 1687 (Fed Cir. 1995).

The present claims are directed to pharmaceutical compositions comprising the $\alpha_2\delta$ subunit calcium channel modulators gabapentin or pregabalin in combination with the antimuscarinics oxybutynin, tolterodine, propiverine, or solifenacin. As described in extensive detail within the present application, Applicants have demonstrated that combinations of $\alpha_2\delta$ subunit calcium channel modulators with antimuscarinics provide a positive synergistic (greater than additive) effect in accepted models of lower urinary tract disorders. This surprising finding

of synergy was demonstrated in multiple experimental examples, as summarized in the following table:

Example	Figures	Combination	Result
1, 2, and 8 (pages 94-105 and 120-123)	2-4 and 18	Gabapentin and Oxybutynin	**Synergy** (page 97, lines 25-30; page 98, lines 5-9 and 21-25; page 102, lines 23-27, page 122, lines 5-7 and 19-22)
3 (pages 105-109)	6 and 8	Pregabalin and Oxybutynin	**Synergy** (page 108, lines 6-11 and 20-24)
4 (pages 109-111)	10	Gabapentin and Tolterodine	**Synergy** (page 111, lines 15-17)
5 (pages 111-114)	12	Pregabalin and Tolterodine	**Synergy** (page 114, lines 4-8)
6 (pages 114-117)	14	Gabapentin and Propiverine	**Synergy** (page 116, lines 26-30)
7 (pages 117-119)	16	Gabapentin and Solifenacin	**Synergy** (page 122, lines 5-7 and 19-22)

As summarized above, synergy was achieved in each of Examples 1-8. In order to assist the Examiner in the interpretation of the experimental results, Applicants will provide a detailed discussion of Example 1 as a guide.

Example 1 describes a study (in a rat model of lower urinary tract disorders) to determine the ability of a combination of gabapentin (an $\alpha_2\delta$ subunit calcium channel modulator) and oxybutynin (an antimuscarinic) to reverse the reduction in bladder capacity caused by continuous infusion of dilute acetic acid. Experimental animals were divided into one of the following three drug administration groups: (1) gabapentin, (2) oxybutynin, or (3) combination (gabapentin + oxybutynin). In order to establish a baseline of bladder capacity, saline was introduced into the bladders of each experimental animal and bladder capacity was measured. Acetic acid was then introduced into the bladders of each experimental animal in order to irritate the bladder and mimic disease conditions, and bladder capacity was again measured. The animals were then administered either gabapentin, oxybutynin, or a combination of the two, and bladder capacity was measured again. This step was carried out for each group using three doses.

Because of the inherent variability in bladder capacities between animals (which could skew results between the groups), the data was normalized to appropriate controls. One control

value was the starting bladder capacity for each group following saline administration (saline control). When the data was normalized to this control, bladder capacity values were presented relative to baseline values ("% saline control index"). This was the index used in Figure 1, and it allowed for an assessment of the gross effects of acetic acid administration on bladder capacity for the different drug administration groups. The % saline control index (Figure 1) shows that acetic acid administration resulted in the same level of reduction in bladder capacity for all groups (approximately 70% less than baseline). However, the % saline control index (Figure 1) would not necessarily show synergistic effects for this experiment because the % saline control index did not directly measure how much each group's bladder capacity increased in response to drug administration.

For a direct measurement of drug effects on bladder capacity, the data must be compared to the bladder capacity level following administration with acetic acid (acetic acid control). Accordingly, the reduced level of bladder capacity following acetic acid administration was then used as a baseline for the purpose of determining the effect of drug treatment on bladder capacity. In other words, when the data was normalized to the acetic acid control, bladder capacity values were presented in terms of how much each group's bladder capacity increased following acetic acid administration ("% recovery from irritation index"). The % recovery from irritation index (Figure 2) was used as the measure of efficacy (see, *e.g.*, page 96, lines 25-26 of the specification), and is the index used in Figure 2.

Using the % recovery from irritation index, the effect of the combination of gabapentin and oxybutynin on bladder capacity improvement was compared to the additive effects that were predicted by the individual drug administration groups. As shown in Figure 2, the combination of gabapentin and oxybutynin produced a synergistic (greater than additive) effect on the recovery of bladder capacity at the low and mid doses. This effect was also described in the specification at lines 22-30 of page 97. This surprising synergistic effect was not suggested by data using the individual drugs.

The detailed discussion provided above demonstrates how synergy was shown in Example 1. However, this synergistic effect was also obtained in Examples 2-8, as summarized in the above table. Thus, the present application describes surprising synergistic effects that

were found using combinations of $\alpha_2\delta$ subunit calcium channel modulators with antimuscarinics in accepted models of lower urinary tract disorders.

The currently marketed antimuscarinic drugs for lower urinary tract disorders are plagued by side effects which include dry mouth, sensitivity to bright light, blurred vision, dry eyes, decreased sweating, flushing, upset stomach, constipation, and drowsiness (see the first full paragraph of page 91 of the specification). One important advantage made possible by the synergistic effect described above for Applicants' novel combination is that a therapeutic effect can be achieved using a lower dose of the antimuscarinic agent than would be required if the antimuscarinic was administered alone. Thus, the undesirable side effects associated with the currently-markted doses of these antimuscarinicss can be avoided. Because the claimed compositions comprising gabapentin or pregabalin in combination with the antimuscarinics oxybutynin, tolterodine, propiverine, or solifenacin provide efficacy while reducing or avoiding such side effects, patient compliance can be significantly improved.

Applicants submit that the evidence described above demonstrating unexpected advantageous results (*i.e.*, positive synergistic effect) for the claimed compositions comprising gabapentin or pregabalin in combination with the antimuscarinics oxybutynin, tolterodine, propiverine, or solifenacin is sufficient to overcome any *prima facie* case of obviousness. Accordingly, Applicants request that this rejection be withdrawn.

Status of Co-Pending Applications

Applicant draws the Examiner's attention to the status of the following co-pending applications. By identifying the status of these applications, Applicant in no way makes any admission as to propriety of the listed rejections or the prior art status of the listed documents, but is instead providing this information for the sake of full disclosure. Applicant further notes that all of the references are of record in the present application or are provided with the concurrently filed information disclosure statement.

U.S. Patent App. No. 10/741,360: Claims 33 and 54-58 were rejected under 35 U.S.C. §102(b) as anticipated by Magistro *et al.* (WO 00/67742) in light of McMichael (U.S. Patent No. 5,610,136), cited to show a fact. Claims 33 and 54-58 were provisionally rejected for

obviousness-type double patenting over claims in U.S. Patent App. No. 10/859,922 and 11/136,183. These rejections were raised in an Office Action mailed October 26, 2007.

U.S. Patent App. No. 10/920,483: Applicants have not received a first Office Action on the merits.

U.S. Patent App. No. 11/136,183: Claims 27-28, 31-32, and 35-36 were rejected under 35 U.S.C. §102(b) as anticipated by Magistro *et al.* (WO 00/67742) in light of Ferguson (EP 0533352), cited to show a fact. Claims 26, 29-30, 33-34, and 37 were rejected under 35 U.S.C. §112, First Paragraph, for lack of written description and enablement. Claims 27-28, 31-32, and 35-36 were provisionally rejected for obviousness-type double patenting over claims in U.S. Patent App. Nos. 10/741,360; 10/859,922; 10/920,483; 11/145,022; 10/805,977; 11/126,062: and 11/598,393.These rejections were raised in an Office Action mailed October 26, 2007.

U.S. Patent App. No. 11/400,554: Claim 35 was rejected under 35 U.S.C. §103(a) as being obvious in light of Segal *et al.* (PCT Pub. No. WO00/61135) in view of Hansen *et al.* (*Southern Medical Journal* 8-9:1051-1059 (2000)). This rejection was raised in an Office Action mailed September 19, 2007.

U.S. Patent App. No. 11/126,062: Claims 20-31 and 39 were rejected under 35 U.S.C. §103(a) as being obvious in light of Kyle *et al.* (U.S. Patent No. 6,974,818). This rejection was raised in an Office Action mailed October 12, 2007.

U.S. Patent App. No. 11/400,666: Claims 44 and 46-47 were rejected under 35 U.S.C. §103(a) as being obvious in light of Abrams (*Expert Opin. Pharmacother.*, 2:1685-1701 (2001)) in combination with Segal *et al.* (PCT Pub. No. WO00/61135). Claims 44 and 46-47 were provisionally rejected for obviousness-type double patenting over claims in U.S. Patent App. Nos. 10/741,360; 10/920,483; 11/400,554; 11/598,393; and 11/126,062. These rejections were raised in an Office Action mailed September 24, 2007.

U.S. Patent App. No. 11/598,393: Applicants have not received a first Office Action on the merits.

CONCLUSION

In view of the aforementioned remarks, Applicants respectfully submit that objections to the specification and claims and the rejections of the claims under 35 U.S.C. §§ 112, Second Paragraph, and 103(a) are overcome. Accordingly, Applicants submit that this application is now in condition for allowance. Early notice to this effect is solicited.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,

Edward R. Ergenzinger
Registration No. 47,549

Customer No. 00826
ALSTON & BIRD LLP
Bank of America Plaza
101 South Tryon Street, Suite 4000
Charlotte, NC 28280-4000
Tel Raleigh Office (919) 862-2200
Fax Raleigh Office (919) 862-2260

"Express Mail" mailing label number EV913518561US

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I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to: Mail Stop Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450

Jennifer Garrison 11/27/07

Jennifer Garrison